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EXAMINER	
HADDAD, MAHER M	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 05/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/032,221	KALLURI, RAGHURAM	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10/18/02 & 3/03/04*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-107* is/are pending in the application.

4a) Of the above claim(s) *43-50,52,53 and 55-107* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-9,15,17-23, 29,31-37,51 and 54* is/are rejected.

7)☒ Claim(s) *2,10-14,16,24-28,30 and 38-42* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/18/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-107 are pending.

2. Applicant's election of Group I, claims 1-42, 51 and 54, drawn to an isolated fragmetn of SEQ ID NO: 10 and SEQ ID NO: 37 as the species, filed on 3/3/04 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Upon reconsideration, Examiner has extended the search to cover SEQ ID NO:38, 39, 40, 41, and 42 recited in claims 10-14, 24-28 and 38-42.

3. Claims 43-50, 52-53 and 55-107 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to nonelected inventions.

4. Claims 1-42, 51 and 54 are under examination as they read on an isolated fragmetn of SEQ ID NO: 10 and SEQ ID NO: 37-42 as the species.

5. The specification on page 1 should be amended to reflect the status of parent application No. 09/625,191, 09/543, 371, 09/479,118 and 09/335,224.

6. The amendment filed 10/18/02, is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: Applicant provides SEQ ID NO: 10 as 244 amino acids rather than 245 amino acid in the claimed provisional applications, However, the corresponding changes to the other sequences contain discrepancies:

Sequence listing and specification

Sequence Name	SEQ ID NO	Original sequence	Amended sequence	Amino acids length	Comments
Tumstatin 333	20	**2-125** of SEQ ID NO: 10	**1-124** of SEQ ID NO:10	124-->124	
Tumstatin 334	21	**126**-*244* of SEQ ID NO:10	**125**-*244* of SEQ ID NO: 10	119--> 120	244 is unchanged
Tum-1	22	*54-244* of SEQ ID NO:10	*54-244* of SEQ ID NO:10	191-->191	delete the 1st aa and add His at aa 19
Tum-2	23	1-132 of SEQ ID NO:10	1-132 of SEQ ID NO:10	132-->132	delete the 1st aa and add Ile at aa 19
Tum-3	24	133-244 of SEQ ID NO:10	133-244 of SEQ ID NO:10	112-->112	delete the 1st aa and add His at aa 19
Tum-4	25	181-244 of SEQ ID NO: 10	181-244 of SEQ ID NO: 10	64-->64	delete the 1st aa and add His at aa 19
Tum-5	26	54-132 of SEQ ID NO: 10	54-132 of SEQ ID NO: 10	79-->79	delete the 1st aa and add Ile at aa 19

T1	27	1-**20** of SEQ ID NO:10	1-**19** of SEQ ID NO:10	20-->19	
T2	28	**54-73** of SEQ ID NO: 10	**53-72** of SEQ ID NO:10	20-->20	
T3	29	**69-88** of SEQ ID NO:10	**68-87** of SEQ ID NO:10	20-->20	
T4	30	**84-103** of SEQ ID NO:10	**83-102** of SEQ ID NO:10	20-->20	
T5	31	**99-117** of SEQ ID NO:10	**98-116** of SEQ ID NO:10	19-->19	
T6	32	**114-132** of SEQ ID NO:10	**113-131** of SEQ ID NO:10	19-->19	
Tumstatin -45-132	33	45-132 of SEQ ID NO:10	45-132 of SEQ ID NO:10	88-->88	delete the 1st aa and add Ile at aa 19
Tumstatin -5-125	34	45-132 of SEQ ID NO:10	45-132 of SEQ ID NO:10	88-->88	delete the 1st aa and add Ile at aa 19
T7	37	**74-98** of SEQ ID NO:10	**73-97** of SEQ ID NO:10	25-->25	
T7 Mutant	38	**74-98** of SEQ ID NO:10	**73-97** of SEQ ID NO:10	25-->25	
T8	39	**69-95** of SEQ ID NO: 10	**68-94** of SEQ ID NO: 10	27-->27	
T8-3	40	**69-95** of SEQ ID NO: 10	**68-94** of SEQ ID NO: 10	27-->27	
TP3	41	**77-95** of SEQ ID NO:10	**76-94** of SEQ ID NO:10	27-->27	
P2	42	**77-95** of SEQ ID NO:10	**76-94** of SEQ ID NO:10	27-->27	
Generic peptide	45	**a hydregen or a peptidyle chain**	**any amino acid**		

The Examiner notices that some subsequences do correspond to the amended SEQ ID NO: 10 while other do not. Further the Examiner notices that all the original sequences refer to unamended SEQ ID NO: 10 (i.e. 245 aa). After the Amendment to SEQ ID NO: 10 (i.e., 244aa) sequences were shifted on either or both the C-terminal and N-terminal without consistency. Other sequences have deletion and insertion of the first and last amino acids. There is selective changes for particular subsequences of SEQ ID NO:10 that do not correspond to amended SEQ ID NO:10. One Skill in the art would only shift all the subsequences of SEQ ID NO: 10 one amino acid toward the N-terminal of SEQ ID NO:10.

Further, The Table on page 47, provides sequences that do correspond the amended SEQ ID NO:10 and sequences that do not correspond to amended SEQ ID NO:10. Such issue carries on all over the specification.

Applicant contends that only T1 has changed, as it originally was presented as beginning with that proline which has been removed with the amendment. However, as seen in the table above several sequences have been change with the amendment.

Applicant is required to cancel the new matter in the reply to this Office action.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is

most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1, 3-9, 15, 17-23, 29, 31-37, 51 and 54 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated fragment of SEQ ID NO: 37, having the ability to inhibit tumor growth, inhibit angiogenesis and inhibit protein synthesis in endothelial cells, SEQ ID NO: 38 having the ability to inhibit protein synthesis in endothelial cells, and SEQ ID NO: 39-42 having the ability to inhibit tumor growth, does not reasonably provide **enablement** for any isolated fragment of SEQ ID NO: 10 having the ability to inhibit tumor growth in claim 1, inhibit angiogenesis in claim 15, or inhibit protein synthesis in endothelial cells in claim 29, wherein the fragment is reduced in claims 3, 17 and 31, wherein the fragment is alkylated in claims 4, 18 and 32, wherein the fragment is oxidized in claims 5, 19 and 33, wherein the protein synthesis is cap-dependent protein synthesis in claim 29, wherein the endothelial cells express the $\alpha v\beta 3$ integrin in claim 54; any isolated mutated fragment of SEQ ID NO: 10, wherein one or more, and five or fewer, amino acids have been substituted, and wherein the mutated fragment has the ability to inhibit tumor growth in claim 6, , to inhibit angiogenic activity in claim 20, or inhibit protein synthesis in endothelial cells in claim 34, wherein the fragment is reduced in claims 7, 21 and 35, wherein the fragment is alkylated in claims 8 , 22 and 35, wherein the fragment is oxidized in claims 9, 23 and 36. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with this claim.

The specification disclosure does not enable one skilled in the art to practice the invention without an undue amount of experimentation.

The specification fails to enable a person of skill in the art to use any fragment derived from Tumstatin to inhibit tumor growth, angiogenesis or protein synthesis in endothelial cells because claim 1 reads on any fragment of Tumstatin molecule The specification offers no guidance as to what particular fragment, other than SEQ ID NO:37 and the mutated fragments 38-42, are required to ensure the induction of tumor growth inhibition, angiogenesis inhibition, and protein synthesis in endothelial cells. A myriad of fragments is encompassed by the claims.

Applicant is relying upon certain biological activities and the disclosure of a single species to support an entire genus. The claims as written encompass a broad genus of fragments with an unlimited number of possibilities with regard to the length of the polypeptide sequence. Further, the enablement issues of making the protein still remain because the specification does not teach and provide sufficient guidance as to which amino acid of SEQ ID NO:10 would have been altered such that the resultant fragment would have retained the function of inhibiting the tumor growth, angiogenesis and protein synthesis in endothelial cells. In addition, fragments derived form SEQ ID NO: 10 provide a range of activities, not all which are necessarily predictive of inhibited ability of tumor growth, angiogenesis and protein synthesis in endothelial cells. For example, Tum-3 does not have anti-tumor cell activity. The specification at page 49, lines 25-29 discloses that the anti-tumor cell activity of region 185-203 is not available when the region is present as part of a full-length folded Tumstatin, or even within a larger Tumstatin fragment (e.g.

within Tum-3). Further the specification on page 51, lines 3-5, discloses that T1 peptide did not inhibit endothelial cell proliferation. Therefore, absent the ability to predict which of these peptides would function as claimed, and given the lack of data on regions critical for activity, for one of skill in the art to practice the invention as claimed would require a level of experimentation that is excessive and undue.

Claims 6, 20 and 34 encompass alterations in the fragments, however, it is recognized in the art that ligands must posses significant structural and chemical complementarity to their target receptors (Kuntz, Science, 1992, Vol. 257:1078-1082, especially page 10709, 2nd col., lines 1-4 and 9-12 under heading "Structure-Based Design) and that ligands generally bind to native states of proteins with little or no interaction with unfolded states (Miller et al, Protein Science, 1997, 6:2166-2179, especially page 2166, 2nd col., lines 18-20) and further that alterations in protein structure lead to alterations in bindings affinity proportional to the magnitude of the alteration (Miller et al, abstract, lines 2-4). Finally, Kuntz teaches that as little as 2% of compounds predicted to inhibit specific enzymztic or receptor systems actually shown inhibition in the micromolar range (page 1080, 3rd col.,). Furthermore, Monboisse *et al* (IDS Ref. No. 67) teach that the sequence S-N-S is unique to the peptide of the α3 chain type IV collagen and substitution of either serine with alanine abolishes the inhibition (see Abstract). Similarly, Han et al (IDS ref. No. 39) teach that serine in position 189 or 191 replacement of α3 chain type IV collagen fragment resulted in reduced ability to inhibit proliferation (see abstract). It would be reasonable to conclude that alterations in fragment would lead to a large alteration in binding affinity.

Reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view on the quantity of experimentation necessary the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

9. Claims 1, 3-9, 15, 17-23, 29, 31-37, 51 and 54 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is in possession of an isolated fragment of SEQ ID NO: 37, having the ability to inhibit tumor growth, inhibit angiogenesis and inhibit protein synthesis in endothelial cells, SEQ ID NO: 38 having the ability to inhibit protein synthesis in endothelial cells, and SEQ ID NO: 39-42 having the ability to inhibit tumor growth.

Applicant is not in possession of any isolated fragment of SEQ ID NO: 10 having the ability to inhibit tumor growth in claim 1, inhibit angiogenesis in claim 15, or inhibit protein synthesis in endothelial cells in claim 29, wherein the fragment is reduced in claims 3, 17 and 31, wherein the fragment is alkylated in claims 4, 18 and 32, wherein the fragment is oxidized in claims 5, 19 and 33, wherein the protein synthesis is cap-dependent protein synthesis in claim 29, wherein the

endothelial cells express the αvβ3 integrin in claim 54; any isolated mutated fragment of SEQ ID NO: 10, wherein one or more, and five or fewer, amino acids have been substituted, and wherein the mutated fragment has the ability to inhibit tumor growth in claim 6, , to inhibit angiogenic activity in claim 20, or inhibit protein synthesis in endothelial cells in claim 34, wherein the fragment is reduced in claims 7, 21 and 35, wherein the fragment is alkylated in claims 8 , 22 and 35, wherein the fragment is oxidized in claims 9, 23 and 36.

Applicant has disclosed only amino acid of SEQ ID NO: 37 to have the claimed activity and the mutants of SEQ ID NO: 38-42; therefore, the skilled artisan cannot envision all the contemplated amino acid sequence possibilities recited in the instant claims. Consequently, conception cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC1993). The Guidelines for the Examination of Patent Application Under the 35 U.S.C.112, ¶ 1"Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 20001, see especially page 1106 3rd column).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 1, 6, 15, 20, 29, 34, 51 and 54 are rejected under 35 U.S.C. 102(b) as being anticipated by Kalluri *et al* (J Biol. Chem. 271:9062-9068, 1996) (IDS Ref. No. 45), as is evidenced by the provisional application 60/126,175 on page 26.

Kalluri *et al* teach a deletion of 26 amino acids in the triple helix and NC1 region (α3/n-26) fragment of the wild type α3(IV) chain. Kalluri *et al* further teach a deletion of N-terminal triple helix 26 aa and C- terminal 36 amino acid (α3/n-26/c-36). Kalluri *et al* further teach mutated fragment, α3/n-26/c-KK having a deletion of N-terminal triple helix 26 aa and substitution of last two lysines to alanines (see the entire document and page 9064 under Figure 1 in particular). While the prior art teachings may be silent as to the ability to "inhibit tumor growth", "inhibit angiogenic activity","inhibit protein synthesis in endothelial cells", the protein synthesis is " cap-dependent protein synthesis" and the endothelia cells "express the αvβ3 integrin" per se; the product in Kalluri *et al* reference is the same as the claimed product. Therefore "inhibit tumor growth", "inhibit angiogenic activity", and "inhibit protein synthesis in endothelial cells" is considered inherent properties. Further, as is evidenced by the provisional application 60/126,175 on page 26, under example 1 that the referenced fragment of NC1 domain (N-terminal deletion) have anti-tumor and angiogenesis activity.

When a claim recites using an old composition or structure (e.g. fragment of SEQ ID NO: 10) and the use is directed to a result or property of that composition or structure (inhibiting tumor growth, angiogenesis and protein synthesis in endothelial cells), then the claim is anticipated. See MPEP 2112.02. Also, see Bristol-Myers Squibb Co. v. Ben Venue Laboratories, Inc. 58 USPQ2d 1508 (CA FC 2001); Ex parte Novitski 26 USPQ 1389 (BPAI 1993); Mehl/Biophile International Corp. V. Milgraum, 52 USPQ2d 1303 (Fed. Cir. 1999); Atlas Powder Co. V. IRECO, 51 USPQ2d 1943 (Fed. Cir. 1999).

The reference teachings anticipate the claimed invention.

12. Claims 1, 6, 15, 20, 29, 34, 51 and 54 are rejected under 35 U.S.C. 102(b) as being anticipated by Monboisse *et al* (J Biol Chem. 269(41):25475-25482, 1994) (IDS Ref. No. 67).

Monboisse *et al* teach four synthetic peptide fragments of NC1 domain of the α3(IV) collagen, α3(IV) 72-89, α3(IV) 104-117, α3(IV) 133-145 and α3(IV) 185-203 fragments (see the entire document and page 25479 under Table II in particular). In addition, Monboisse *et al* teach mutated fragments of NC1 domain of the α3(IV) collagen, α3(IV) H 185-203, wherein serine residue 189 was substituted with alanine ($S \rightarrow A^{189}$), and fragment α3(IV) B 185-203, wherein serine residue 191 was substituted with alanine ($S \rightarrow A^{191}$) among others (see page 25480, Table III in particular) While the prior art teachings may be silent as to the ability to "inhibit tumor growth", "inhibit angiogenic activity", "inhibit protein synthesis in endothelial cells", the protein synthesis is " cap-dependent protein synthesis" and the endothelia cells "express the αvβ3 integrin" per se; the product in Monboisse *et al* reference is the same as the claimed product. Therefore "inhibit tumor growth", "inhibit angiogenic activity", and "inhibit protein synthesis in endothelial cells" is considered inherent properties.

When a claim recites using an old composition or structure (e.g. fragment of SEQ ID NO: 10) and the use is directed to a result or property of that composition or structure (inhibiting tumor growth, angiogenesis and protein synthesis in endothelial cells), then the claim is anticipated. See MPEP 2112.02. Also, see Bristol-Myers Squibb Co. v. Ben Venue Laboratories, Inc. 58 USPQ2d 1508 (CA FC 2001); Ex parte Novitski 26 USPQ 1389 (BPAI 1993); Mehl/Biophile International Corp. V. Milgraum, 52 USPQ2d 1303 (Fed. Cir. 1999); Atlas Powder Co. V. IRECO, 51 USPQ2d 1943 (Fed. Cir. 1999).

The reference teachings anticipate the claimed invention.

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

14. Claims 1, 3, 6-7, 15, 17, 20-21, 29, 31 and 34-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kalluri *et al* (J Biol. Chem. 271:9062-9068, 1996) (IDS Ref. No. 45) or Monboisse *et al* (J Biol Chem. 269(41):25475-25482, 1994) (IDS Ref. No. 67) each in view of U.S. Patent 5,858,670.

The teachings of Kalluri et al and Monboisse et al references have been discussed, supra

The claimed invention differs from the reference teachings only by the recitation that the fragment is reduced.

The `670 patent teaches that a reduced peptide bond may be introduced as a dipeptide subunit. Such a molecule would be resistant to peptide bond hydrolysis, e.g., protease activity. (Col., 10 lines 50-61 in particular).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to produce the fragments taught by Kalluri et al and Monboisse et al as reduced fragment as taught by `670 patent.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because such reduced fragments would be resistant to peptide bond hydrolysis as taught by the `670 patent.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

15. Claims 1, 4, 6, 8, 15, 18, 20, 22, 29, 32, 34 and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kalluri *et al* (J Biol. Chem. 271:9062-9068, 1996) (IDS Ref. No. 45) or Monboisse *et al* (J Biol Chem. 269(41):25475-25482, 1994) (IDS Ref. No. 67) each in view of U.S. Patent 5,326,875.

The teachings of Kalluri et al and Monboisse et al references have been discussed, supra

The claimed invention differs from the reference teachings only by the recitation that the fragment is alkylated.

The `875 patent teaches that alkylated peptides can be purified by crystallization or by silica gel chromatography. Further the `875 patent teaches that proteced alkylated peptides are readily soluble in acidic aqueous medium (Col., 3 lines 43-68 in particular).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to produce the fragments taught by Kalluri et al and Monboisse et al as alkylated fragment as taught by `875 patent.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because such alkylated fragments are readily soluble in acidic aqueous medium as taught by the `670 patent.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

16. Claims 1, 5, 6, 9, 15, 19-20, , 23, 29, 33-34 and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kalluri *et al* (J Biol. Chem. 271:9062-9068, 1996) (IDS Ref. No. 45) or Monboisse *et al* (J Biol Chem. 269(41):25475-25482, 1994) (IDS Ref. No. 67) each in view of U.S. Patent 5807,821.

The teachings of Kalluri et al and Monboisse et al references have been discussed, supra

The claimed invention differs from the reference teachings only by the recitation that the fragment is oxidized.

The `821 patent teaches that a variety of protecting groups can be incorporated into the synthesis of linear peptide to facilitate isolation, purification, and/or yield of the desired peptide. Protection of cysteine residues found in the peptide can be accomplished using, for example, a triphenylmethyl, acetamidomethyl and/or 4-methoxybenzyl group in any combination. Such a strategy may offer advantages for subsequent oxidation studies to yield folded peptide. (Col., 8 lines 45-60 in particular).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to produce the fragments taught by Kalluri et al and Monboisse et al as oxidized fragment as taught by `821 patent.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because such oxidation of the peptide offer advantages for subsequent oxidation studies to yield folded peptide as taught by the `821 patent.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

17. Claims 2, 10-14, 16, 24-28, 30, 38-42 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Maher Haddad, Ph.D.
Patent Examiner
Technology Center 1600
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